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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,745	12/21/2001	Keiichi Kawai	Q67507	2602

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EXAMINER
JONES, DAMERON L

ART UNIT	PAPER NUMBER
1616	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/018,745	Applicant(s) KAWAI ET AL.	
	Examiner D. L. Jones	Art Unit 1616	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/21/01; 11/18/02; and 4/10/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17,18-29* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

ACKNOWLEDGMENTS

1. The Examiner acknowledges Paper No. 4, filed 12/21/01, wherein claims 1-13 were canceled and claims 14-29 were added.

Note: Claims 14-29 are pending.

APPLICANT'S INVENTION

2. The instant invention is directed to pharmaceutical compositions, kits, and methods thereof having a first drug and a second drug wherein the second drug is administered simultaneously, before, or after the first drug.

RESPONSE TO APPLICANT'S ELECTION

3. Applicant's election of Group XV directed to claims 14-29 comprising a composition, kit, and method thereof wherein a first drug in combination with a second drug (verapamil) is used is acknowledged in Paper No. 7, filed 4/10/03. In addition, the Examiner acknowledge of the species wherein the first drug is N-isopropyl-p-iodoamphetamine (IMP) and the radionuclide is I-123. Since Applicant did not point out the supposedly errors in the restriction requirement, the election is viewed as an election without traverse. Hence, the restriction requirement is still deemed proper and is therefore made FINAL.

Note: Initially, the Examiner searched for Applicant's elected species. However, since no prior art could be found to reject Applicant's species, the search was extend over the full scope of the elected group. The search has not been extended beyond

Applicant's elected Group. Thus, Applicant is respectfully requested to cancel all non-elected subject matter.

112 REJECTIONS (First Paragraph)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 19 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds selected from bisaminothiol, monaminomonoamidobisthiol, bisamidobisthiol, mercaptoacetylglycylglycylglycine, hexamethylpropyleneamineoxime, ethylenebis[bis(2-ethoxyethyl)phosphine], 2,3-dimercaptosuccinic acid, ethylenecysteine dimer, methoxyisobutylisonitrile, polyamine, pyriodoxyldeneaminate, methylene disphosphonate, hydroxymethylene disphosphonate, beta methyl omega phenylpentadecanoic acid, N-isopropylamphetamine, hippuric acid, benzylguanidine, and tropane, does not reasonably provide enablement for derivatives of the compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are several guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation. The factors to be considered in determining what constitutes undue

experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples; the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims. In particular, the specification fails to enable the skilled artisan to practice the invention without undue experimentation wherein any compounds derived from the group of agents above are utilized.

The disclosure of the present invention is drawn to compositions, kits, and methods thereof comprising a first and second drug wherein the second drug is verapamil, as defined in Applicant's elected invention. While a skilled artisan would be motivated to select an agent from the *specific* ones listed by Applicant (i.e., bisaminothiol, monaminomonoamidobisthiol, bisamidobisthiol, mercaptoacetylglycylglycylglycine, hexamethylpropyleneamineoxime, ethylenebis[bis(2-ethoxyethyl)phosphine], 2,3-dimercaptosuccinic acid, ethylenecysteine dimer, methoxyisobutylisonitrile, polyamine, pyriodoxyldeneaminate, methylene disphosphonate, hydroxymethylene disphosphonate, beta methyl omega phenylpentadecanoic acid, N-isopropylamphetamine, hippuric acid, benzylguanidine, and tropane), the artisan would not know what derivatives Applicant is referring to which would be compatible with the instant invention. Hence, a skilled artisan in the art would not be able to readily ascertain the unlimited number of compounds derived or obtained from known or hypothetical agents and containing essential elements of the parent agents. Thus, the skilled artisan would be forced to randomly test various derivatives of the agents in order to determine which derivatives possess chemical properties which would yield similar results as that obtained when using the specific agents set forth

above. Furthermore, the amount of guidance present in the specification fails to present the necessary instruction to determine what derivatives are encompassed by the claims.

The specification does not provide guidance as to any specific substances which are compatible with the instant invention nor does the specification disclose specific characteristics for such substances. In addition, the specification fails to provide guidance as to how any agent should be modified to generate the derivative(s). No working examples are provided to provide such missing information. Without such information, one skilled in the art could not predict which substances out of the vast number of known and hypothetical substances are encompassed by Applicant's phrase "or its derivatives". Therefore, due to the lack of guidance and the amount of experimentation required to identify any compounds that are derivatives of the agents above, agents other than bisaminothiol, monaminomonoamidobisthiol, bisamidobisthiol, mercaptoacetylglycylglycylglycine, hexamethylpropyleneamineoxime, ethylenebis[bis(2-ethoxyethyl)phosphine], 2,3-dimercaptosuccinic acid, ethylenecysteine dimer, methoxyisobutylisonitrile, polyamine, pyriodoxyldeneaminate, methylene disphosphonate, hydroxymethylene disphosphonate, beta methyl omega phenylpentadecanoic acid, N-isopropylamphetamine, hippuric acid, benzylguanidine, and tropane are not properly enabled by the instant specification.

112 REJECTIONS (Second Paragraph)

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 19 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "or its derivatives" (or "analog") is indefinite because one of ordinary skill in the art would not be able to readily ascertain the vast number of compounds derived or obtained from known or hypothetical agents and containing essential element of the parent agents that are encompassed by the instant invention.

102 REJECTIONS

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 14-17, 20, 21, 23, 25, 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Pritchard et al (J. Clin. Pharmacol., 1985, Vol. 25, pages 347-353).

Pritchard et al disclose plasma protein binding of bepridil using radiolabeled bepridil (bepridil-14C). The free fractions of bepridil were enhanced by the addition of verapamil (see entire document, especially, abstract; page 348, column 2, 'Effects of Other Drugs'; page 351, 'Table V'). In addition, Pritchard et al disclose that the addition of verapamil at ten- to 100-fold molar excess over bepridil resulted in significant

displacement of bepridil from its plasma protein binding sites (page 351, column 1, first complete paragraph).

Thus, both Applicant and Pritchard et al disclose a pharmaceutical composition wherein a first drug (bepridil) is administered prior to the administration of verapamil.

10. Claims 14-17, 20, 21, 23, 25, 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Somogyi et al (Br. J. Clin. Pharmac., 1981, Vol. 12, pages 51-60).

Somogyi et al disclose the pharmacokinetics, bioavailability, and ECG response of verapamil in seven patients with liver cirrhosis using stable labeled techniques wherein both an intravenous and oral dose of verapamil are administered simultaneously (see entire document, especially, abstract). In addition, Somogyi et al disclose (1) that a stable *labeled* (14C-verapamil) oral solution of verapamil is administered simultaneous with and *unlabeled* intravenous dose of the drug (page 51, column 2, first complete paragraph; page 52, columns 1 and 2, bridging paragraph; page 52, column 2, 'Plasma protein binding and erythrocyte distribution'; page 55, Figure 1 and 2). (2) Antipyrine was administered to patients as an oral solution. Likewise, indocyanine green was administered as a bolus dose (page 52, column 2, first complete paragraph). Furthermore, Somogyi et al disclose that most of the patients in their study were receiving cimetidine and/or spironolactone. The coadministration of cimetidine and/or spironolactone with verapamil may have affected the bioavailability and oral clearance of verapamil (page 59, column 2, first complete paragraph).

Thus, both Somogyi et al and Applicant disclose a pharmaceutical composition wherein a first drug (cimetidine and/or spironolactone) is administered prior to the administration of verapamil. Also, Somogyi et al disclose the simultaneous administration of labeled and unlabeled verapamil to a subject.

Note: It is duly noted that Applicant's independent claims do not specify that the same drug may not be administered in different forms as the first and second drugs (e.g., an unlabeled and labeled form of the same compound could very well be considered to be two separate drugs). Also, it should be noted that Somogyi et al disclose that most of the patients in their study were receiving cimetidine and/or spironolactone and that the coadministration of those drugs with verapamil may have affected the bioavailability and oral clearance of verapamil.

103 REJECTIONS

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 14 and 16-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pritchard et al (J. Clin. Pharmacol., 1985, Vol. 25, pages 347-353) in view of Li et al (US Patent No. 5,977,163).

Pritchard et al (see discussion above) fail to disclose a kit comprising the first and second drug and other radiolabels and/or a chelator which may be conjugated to the drug.

Li et al disclose water-soluble prodrugs (see entire document, especially, abstract). The methods disclosed by Li et al may be used to generate a water-soluble polymer conjugate of other therapeutic drugs which include verapamil (column 2, lines 56-68). The complexes may be radiolabeled with various metals (columns 3-4, bridging paragraph). Likewise, the complexes may be conjugated to various chelator including DTPA, DOTA, TETA, SMSA, DTTP, HEDP, and DPDP to name a few (column 4, lines 4-17). The complexes of Li et al may be imaged using single photo emission computer topography or positron emission tomography (column 8, lines 34-47) or another method depending upon the nuclide selected (columns 3-4, bridging paragraph; column 8, lines 52-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Pritchard et al using the teachings of Li et al and generate a kit comprising the first and second drug and attach various radiolabels and/or a chelator to the drug composition because Li et al disclose a composition wherein verapamil may be added to generate a water soluble polymer conjugate. Conjugates may be radiolabeled with aluminum, boron, calcium, copper, gadolinium, gallium, indium, iron, rhenium, samarium, technetium, thallium, yttrium, zinc, and tin to name a few metals. Likewise, it would be obvious to incorporate a chelator since Li et al disclose that possible chelators, include but are not limited to ,

DTPA, DOTA, TETA, SMSA, DTTP, HEDP, and DPDP to name a few. Also, it should be noted that it would be obvious to a skilled practitioner to label the complex with carbon-11 since both carbon-14 and carbon-11 are radioisotopes of carbon and Li et al disclose that the subject may be imaged using single photon emission computer tomography or positron emission tomography. Furthermore, it is noted that since both Pritchard et al and Li et al disclose the use of verapamil in combination with another drug that may be radiolabeled, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

13. Claims 14 and 16-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Somogyi et al (Br. J. Clin. Pharmac., 1981, Vol. 12, pages 51-60) in view of Li et al (US Patent No. 5,977,163).

Somogyi et al (see discussion above) fail to disclose a kit comprising the first and second drug and other radiolabels and/or a chelator which may be conjugated to the drug.

Li et al (see discussion above).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Somogyi et al using the teachings of Li et al and generate a kit comprising the first and second drug and attach various radiolabels and/or a chelator to the drug composition because Li et al disclose a composition wherein verapamil may be added to generate a water soluble polymer conjugate. Conjugates may be radiolabeled with aluminum, boron, calcium, copper,

gadolinium, gallium, indium, iron, rhenium, samarium, technetium, thallium, yttrium, zinc, and tin to name a few metals. Likewise, it would be obvious to incorporate a chelator since Li et al disclose that possible chelators, include but are not limited to , DTPA, DOTA, TETA, SMSA, DTTP, HEDP, and DPDP to name a few. Also, it should be noted that it would be obvious to a skilled practitioner to label the complex with carbon-11 since both carbon-14 and carbon-11 are radioisotopes of carbon and Li et al disclose that the subject may be imaged using single photon emission computer tomography or positron emission tomography. Furthermore, it is noted that since both Somogyi et al and Li et al disclose the use of verapamil in combination with another drug that may be radiolabeled, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

SPECIFICATION

14. This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading "This application is a 371 of PCT/JP00/04039, filed 6/21/00." should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of all nonprovisional parent applications referenced should be included.

COMMENTS/NOTES

15. In order to clarify the claims, the Examiner respectfully suggests the following:

(1) Claim 17, line 2, replace 'raiodiagnostic' with 'radiodiagnostic';

(2) Claim 22, line 2, replace 'separately filled in a' with 'in a separate'; and

(3) Claim 22, line 2, delete 'form for supply'.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose' Dees can be reached on (703) 308- 4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

June 19, 2003